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| 10/049,849 | 06/27/2002 | William Hugold Velander | TRANS 1 | 2472 |

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| EXAMINER |
|---|
| HAMA, JOANNE |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/049,849 | VELANDER, WILLIAM HUGOLD | |
| | Examiner | Art Unit | |
| | Joanne Hama, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5-8,11-13,16,17,20,22,24,25,27,40,42,44,46,53,56-59 and 61* is/are pending in the application.

4a) Of the above claim(s) *1,5-8,11-13,16,17,20,22,24,25,27,53 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *40,42,44,46,56-58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant filed a response to the Non-Final Action of April 23, 2007 on July 19, 2007. Claims 2-4, 9, 10, 14, 15, 18, 19, 21, 23, 26, 28-39, 41, 43, 45, 47-52, 54, 55, 60 are cancelled. Claims 1, 5-8, 11-13, 16, 17, 20, 22, 24, 25, 27, 53, 59 are withdrawn. Claims 40, 44, 61 are amended.

Claims 40, 42, 44, 46, 56-58, 61 are under consideration.

This application contains claims 1, 5-8, 11-13, 16, 17, 20, 22, 24, 25, 27, 53, 59, drawn to an invention nonelected with traverse in the reply filed on November 17, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

***Withdrawn Rejections***

***35 U.S.C. § 112, 1st parag., Enablement***

Applicant's arguments, see page 7 of Applicant's response, filed July 19, 2007, with respect to the rejection of claims 40, 42, 44, 46, 56-58, 60, 61 have been fully considered and are persuasive. Applicant indicates that claims 40 and 44 have been amended to remove the partial identity limitations. The rejection of claims 40, 42, 44, 46, 56-58, 61 has been withdrawn. It is noted that the rejection of claim 60 is withdrawn as the claim has been cancelled.

***35 U.S.C. § 112, 1st parag., Written Description***

Applicant's arguments, see pages 7-8 of Applicant's response, filed July 19, 2007 with respect to the rejection of claims 40, 42, 44, 46, 56-58, 60, 61 have been fully

considered and are persuasive. Applicant has amended claims 40 and 44 to remove "% identical" language from the claims. The rejection as it applies to this issue is withdrawn. With regard to claims 60 and 61, Applicant indicates that claim 61 has been amended to recite that prothombin activity results in the production of prothombin. The rejection of claims 40, 42, 44, 46, 56-58, 61 has been withdrawn. The rejection of claim 60 is withdrawn as the claim has been cancelled.

***35 U.S.C. § 112, 2nd parag.***

With regard to the rejection of claim 61 for being indefinite, Applicant's claim amendment, filed July 19, 2007, has been fully considered and is persuasive. The claim had recited a sequence to be "at least 100% identical to said human prothrombin amino acid sequence," and was unclear as to how a sequence could have an upper limit of identity that is more than 100%. Applicant has amended the claim indicating that the sequence is "100% identical to said human prothrombin amino acid sequence." The rejection of claim 61 has been withdrawn.

## ***Maintained Rejections***

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, and in view of van Cott and Velander, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690, for reasons of record, April 23, 2007.

Applicant's arguments filed July 19, 2007 have been fully considered but they are not persuasive.

With regard to the Butler reference, Applicant indicates that the statement made by the Examiner regarding the reference merely identifies a problem in the art that requires solving. The Examiner, in fact, admits this very fact by stating that Butler does not teach making recombinant human prothrombin in the milk of transgenic mammal. Applicant's specification has solved the above problem; Butler does not, even when referring to one of the Applicant's previous publication, Velander et al., 1996. As such, Butler does not provide any articulated reasoning as to how to approach the problem (Applicant's response, page 10). In response, this is not persuasive. Butler is not being used in a 102 rejection. Butler is used in a 103 rejection and is used to demonstrate that recombinant proteins were expressed in milk of transgenic mammals at the time the invention was made. Butler demonstrates that recombinant fibrinogen can be expressed in the milk of transgenic mammals. Butler does not teach that recombinant prothrombin was expressed in the milk of transgenic mammals, but does indicate that other recombinant plasma-derived proteins, such as prothrombin, could be expressed in the milk of transgenic mammals. Butler indicates that expression of recombinant proteins in

milk is pathogen-free and can be made in large quantities (Office Action, April 23, 2007). As such, Butler provides motivation to express recombinant proteins in milk, and also specifically indicates that the system of expressing recombinant proteins in milk can be used to express recombinant plasma-derived proteins, particularly, prothrombin.

Applicant indicates that Teleflex clearly expects an Examiner to provide an argument based upon scientific facts extracted from the scientific reference. Neither Butler nor Jorgensen et al. provide any scientific facts regarding the construction of a transgenic pig that secretes prothrombin in milk (Applicant's response, page 10). In response, the Examiner has provided scientific facts extracted from the scientific references which were used to illustrate that upon reading the combination of the references, an artisan would have arrived at the claimed invention. Butler was used to illustrate that recombinant fibrinogen was expressed in the milk of transgenic mice and sheep. Butler teaches that the system could be modified to express other plasma-derived proteins, such as prothrombin. At the time of filing, the art teaches that artisans were actively using other recombinant expression systems to express prothrombin (Jorgensen et al., 1987). Jorgensen et al.'s teaching indicates that the sequence of human prothrombin was known at the time of filing and that recombinant prothrombin was actively being pursued in the art. The motivation to combine the two teachings was given by Butler who teaches that the system of expressing recombinant proteins in milk has advantages over other expression systems. These advantages are that the recombinant protein is produced abundantly and that the recombinant protein is pathogen-free. As for arriving at prothrombin that has a completely gamma-carboxylated Gla domain (as claimed in claim 40), neither Butler nor Jorgensen et al. provide any guidance that human

prothrombin would have been completely gamma-carboxylated Gla domain. However, at the time of filing, van Cott and Velander, 1998, teach that pigs could gamma-carboxylate recombinant proteins and thus, an artisan would have been motivated to use a pig to express human prothrombin.

Applicant indicates that Jorgensen et al. is a cited reference that is limited to in vitro cell culture protein expression in an unsuccessful attempt to teach Butler's admitted deficiency of not teaching making recombinant human prothrombin in the milk of a transgenic mammal. Jorgensen et al. does not teach any concepts related to transgenic animals. Thus, the Examiner's combination of Butler and Jorgensen et al. also fails to teach the making of recombinant human prothrombin in the milk of a transgenic mammal (Applicant's response, pages 10-11). In response, this is not persuasive. As indicated above, Butler teaches a system used to express recombinant proteins in the milk of a transgenic mammal. Jorgensen et al. teach that at the time of filing, artisans were actively making recombinant human prothrombin. An artisan would have combined the teachings of Butler and Jorgensen et al. in order to arrive at a mammal expressing human prothrombin in milk because Butler points out that his system would be a good system to express plasma-derived proteins, particularly prothrombin. The system is good for expressing recombinant proteins because the system expressed recombinant proteins in large quantities and the system is pathogen-free.

Applicant indicates that Butler provides not guidance and/or evidence (much less data) providing any steps that should be taken to produce a transgenic pig that secretes prothrombin in milk. Applicant indicates that because Butler taught that "human fibrinogen was expressed in large quantities in milk" that this alone constitutes a

reasonable expectation of success that human prothombin would also be expressed in large quantities. Applicant indicates that the Examiner has no legal or scientific basis for making these conclusory statements. In response, Butler indicating that steps should be taken to produce a transgenic pig that secretes prothromin in milk was not used as a 102 reference. Rather, Butler was used to illustrate that mammals could be used to express recombinant proteins in milk. van Cott and Velander was used to illustrate that pigs were used to express recombinant proteins and that recombinant proteins expressed from pigs could gamma-carboyxylate proteins. As such, an artisan could use the combined teachings of Butler, Joregensen et al., and van Cott and Velander to arrive at the claimed invention. As for Applicant indicating that the Examiner has no legal or scientific basis for making conclusory statements that human prothrombin would be expressed in large quantities. In response, the Examiner relied upon Butler who provides scientific guidance that the method he describes can be adapted for use of other proteins. Further, Butler had indicated that his method can be used to make prothrombin. As such, an artisan would rely upon Butler for providing guidance that the method has other applications.

Applicant indicates that by making these conclusory statements, the Examiner has not provided evidence as to why a skilled artisan would make the combination. The Examiner has stated what the Examiner believes each references teaches in isolation from the other reference and then stated it would be obvious to combine the elements. In order to support the combination, the Examiner has relied upon the level of the skill in the art (Applicant's response, page 11). In response, this is not persuasive. As discussed above, all elements used to arrive at the claimed invention were known to an artisan of ordinary

skill in the art. Butler teaches a method of expressing recombinant protein in a transgenic mammal's milk; Jorgensen et al. teaches that in vitro methods of making recombinant human prothrombin was known in the art; and van Cott and Velander teach that expressing recombinant proteins in pigs were known to produce gamma-carboxylated proteins. As such, an artisan would have taken the transgene used in making recombinant human prothrombin and used it in the method described by Butler. An artisan would have also carried out the method in a pig, given the teachings of van Cott and Velander.

Applicant indicates that Jorgensen et al. does not provide reasonable expectation of success that the disclosed plasmids are useful at high expression levels. Consequently, Jorgensen et al. provides a clear teaching away to use the disclosed plasmids for high yield expression platforms. As such, the combination with Butler fails. Applicant also indicates that the van Cott publication does not provide any evidence that the plasmids provided in Jorgensen would be fully carboxylated in a high yield system (Applicant's response, page 12). In response, the Office Action indicated that it would have been obvious for an artisan to substitute the nucleic acid encoding human prothrombin with that of fibrinogen (Office Action, April 23, 2007, page 11) and not expression construct for expression construct. As such, an artisan would have arrived at the claimed invention in expressing human prothrombin in the milk of a transgenic mammal. With regard to van Cott not indicating whether or not any of the plasmids provided by Jorgensen would be fully carboyxlated in a high yield system, the point that the Examiner was making regarding the teaching of van Cott was that recombinant proteins made in the milk of transgenic pigs are gamma-carboxylated. As such, there is reasonable expectation of

success that human prothrombin expressed using Butler's system would be gamma-carboxylated if expressed in the milk of transgenic pigs.

Applicant points out that the Examiner made an erroneous statement that, "one would have been motivated to use the system taught by Butler because there is a higher yield of prothrombin in milk (5g/liter) than in a mammalian cell expression system (0.55ug/ml)." Applicant indicates that the Examiner has improperly substituted "prothrombin" for "fibrinogen" when discussing Butler and that the Examiner has admitted that Butler did not make prothrombin. Applicant indicates that the teachings of van Cott and Jorgensen cannot be combined with Butler because fibrinogen is not gamma-carboxylated. Thus, the Examiner's prediction that Butler could produce 5g/liter of prothrombin because one ewe produced 5 g/liter of fibrinogen is completely unsupportable. (Applicant's response, page 12). In response, the Examiner had used "5g/liter" to illustrate the amount of recombinant protein that could be expressed in the milk of a transgenic mammal, as compared to an in vitro system. Applicant is correct that "5g/liter" refers to that of fibrinogen made by Butler and Butler also teaches that one ewe made 0.5g/liter (Butler, page 8). However, the main point that was being made is that there is a large difference in amount of recombinant protein produced in the milk of transgenic mammals versus an in vitro system. The system taught by Butler produces recombinant protein in the amount of g/liter; the system taught by Jorgensen produces mg/liter. As such, an artisan would have been motivated to use Butler's system which produces 1000 times more protein. As for the teachings of van Cott and Jorgensen cannot be combined with Butler because fibrinogen is not gamma-carboxylated, whether or not fibrinogen is gamma-carboxylated does not play a role in determining whether an

artisan would have expressed prothrombin in the in the milk of mammals. Rather, an artisan would take Butler's method of expressing recombinant protein in milk of a transgenic mammal and substitute the coding region for fibrinogen with that of human prothrombin. In addition to this, it is noted that Butler also indicates that his method can be used with prothrombin. As for using transgenic pigs to make the recombinant prothrombin, there is no requirement that an artisan use pigs to practice the claimed invention. van Cott and Velander teach that mice are not as good as pigs in gamma-carboxylating recombinant proteins. As such, an artisan could reasonably expect that any transgenic mammal could produce gamma-carboxylated prothrombin and that some mammals would be better than others. However, should an artisan want to produce more gamma-carboxylated prothrombin, an artisan would have used pigs, as taught by van Cott and Velander. As for motivation for wanting more gamma-carboxylated prothromin, Jorgensen et al. teach that gamma-carboxylation of prothrombin is important for prothrombin binding to phospholipid surfaces and for coagulant activity (Jorgensen et al., page 6729, 1st col. Introduction to 2nd col., 1st parag.). As such, an artisan would have been motivated to use pigs in order to arrive at gamma-carboxylated prothrombin.

Thus, the claims remain rejected.

It is noted that the rejection of claim 60 is withdrawn as the claim is cancelled.

Claims 40, 42, 44, 46, 56, and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry,

262: 6729-6734, and in view of Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, for reasons of record, April 23, 2007.

Applicant's arguments filed July 19, 2007 have been fully considered but they are not persuasive.

Applicant indicates that Butler and Jorgensen et al. fail to create the Applicant's claimed invention (Applicant's response, page 13). In response, as described above, the art teaches the elements that can be used to arrive at the claimed invention. Further, the art indicates motivation for an artisan to combine the teachings to arrive at the claimed invention.

Applicant indicates that Le Bonniec et al. provides no information sufficient to fulfill the deficiencies of Butler and Jorgensen et al. to fulfill the identified deficiencies of Butler and Jorgensen et al. to Applicant's independent claims. Because Butler and Jorgensen et al. fail as a proper combination, the teachings of Le Bonniec et al. to a dependent claim are irrelevant (Applicant's response, page 13). In response, this is not persuasive. As indicated above, the art teaches the elements that can be used to arrive at the claimed invention. Further, the art indicates motivation for an artisan to combine the teachings to arrive at the claimed invention.

Thus, claims 40, 42, 44, 46, 56, and 58 remain rejected.

Claims 40 and 57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA, in view

of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, in view of Seegers et al., 1950, Blood 5: 421-433, for reasons of record, April 23, 2007.

Applicant's arguments filed July 19, 2007 have been fully considered but they are not persuasive.

Applicant indicates that Butler and Jorgensen et al. fail to create the Applicant's claimed invention (Applicant's response, page 13). In response, as described above, the art teaches the elements that can be used to arrive at the claimed invention. Further, the art indicates motivation for an artisan to combine the teachings to arrive at the claimed invention.

Applicant indicates that Seegers et al. provides no information sufficient to fulfill the deficiencies of Butler and Jorgensen et al. to fulfill the identified deficiencies of Butler and Jorgensen et al. to Applicant's independent claims. Because Butler and Jorgensen et al. fail as a proper combination, the teachings of Seegers et al. to a dependent claim are irrelevant (Applicant's response, page 13). In response, this is not persuasive. As indicated above, the art teaches the elements that can be used to arrive at the claimed invention. Further, the art indicates motivation for an artisan to combine the teachings to arrive at the claimed invention.

Thus, claims 40 and 57 remain rejected.

***Conclusion***

No claims allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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Joanne Hama
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